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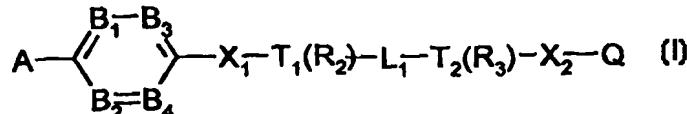
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(54) Title: HETEROCYCLIC DERIVATIVES WHICH INHIBIT FACTOR XA

(57) Abstract

The invention relates to heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect, formula (I).



or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect, formula (I).

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HETEROCYCLIC DERIVATIVES WHICH INHIBIT FACTOR XA

The invention relates to heterocyclic derivatives, or pharmaceutically-acceptable salts thereof, which possess antithrombotic and anticoagulant properties and are accordingly 5 useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of the heterocyclic derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect.

The antithrombotic and anticoagulant effect produced by the compounds of the 10 invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

15 Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by R.B. Wallis, Current Opinion in Therapeutic Patents, 1993, 1173-1179. Thus it is known that two proteins, one known as antistatin and the other known as tick anticoagulant protein (TAP), are specific Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

20 It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by R.B. Wallis, all possessed a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that certain heterocyclic derivatives possess Factor Xa inhibitory activity. Many of the compounds of the present invention also possess the 25 advantage of being selective Factor Xa inhibitors, that is the enzyme Factor Xa is inhibited strongly at concentrations of test compound which do not inhibit or which inhibit to a lesser extent the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

The compounds of the present invention possess activity in the treatment or 30 prevention of a variety of medical disorders where anticoagulant therapy is indicated, for example in the treatment or prevention of thrombotic conditions such as coronary artery and

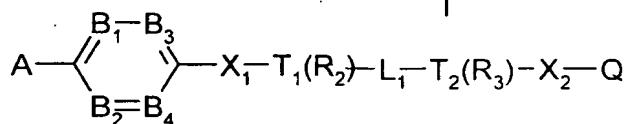
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cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular injury including reocclusion and restenosis following angioplasty and coronary artery bypass 5 surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood, cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischaemia and angina (including unstable angina).

The compounds of the invention are also useful as inhibitors of blood coagulation in 10 an ex-vivo situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

Accordingly in one aspect the present invention provides compounds of the formula

I



15

wherein:

A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur atoms;

B₁, B₂, B₃ and B₄ are independently CH or a nitrogen atom, wherein the ring formed from B₁,

20 B₂, B₃ and B₄ may optionally be substituted; with the proviso that at least one of B₁, B₂, B₃ and B₄ is nitrogen;

T₁ is CH or N;

T₂ is CH or N;

with the proviso that at least one of T₁ and T₂ is N;

25 X₁ is SO, SO₂, C(R₄)₂ or CO when T₁ is CH or N; or in addition X₁ is O or S when T₁ is CH; and wherein each R₄ is independently hydrogen or (1-4C)alkyl;

L₁ is (1-4C)alkylene or (1-3C)alkylenecarbonyl;

R₂ is hydrogen or (1-4C)alkyl;

R₃ is hydrogen or (1-4C)alkyl;

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or R₂ and R₃ are joined to form a C₁₋₄alkylene or -CH₂CO- group; wherein the ring formed by T₁, R₂, R₃, T₂ and L₁ is optionally substituted;
X₂ is S(O)_y wherein y is one or two, C(R⁵)₂ or CO; and each R⁵ is hydrogen or (1-4C)alkyl;
Q is phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl or a
5 heterocyclic moiety containing up to 4 ring heteroatoms selected from nitrogen, oxygen and
sulphur and Q is optionally substituted;
and pharmaceutically acceptable salts thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight 10 chain version only. An analogous convention applies to other generic terms.

It is to be understood that certain heterocyclic derivatives of the present invention can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Factor Xa inhibitory activity.

15 It is further to be understood that, insofar as certain of the compounds of the formula defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention encompasses any such optically active or racemic form which possesses Factor Xa inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for 20 example by synthesis from optically active starting materials or by resolution of a racemic form.

Preferably A is a pyridyl, pyrimidinyl or pyridazinyl ring for example 4-pyridyl, 2-pyridyl, 4-pyridazinyl, 3-pyrimidinyl, 4-pyrimidinyl or 3-pyridyl. Of these 4-pyrimidinyl, 4-pyridazinyl and 4-pyridyl are most preferred.

25 In one aspect A is unsubstituted. In another aspect A is substituted by one, two or three atoms or groups selected from halo (for example fluoro, chloro or bromo), trifluoromethyl, cyano, amino, oxo, hydroxy, nitro, (1-4C)alkyl (for example methyl or ethyl), C₁₋₄alkoxy (for example methoxy or ethoxy), (1-4C)alkylamino (for example methylamino or ethylamino) or di-(1-4C)alkylamino (for example dimethylamino or diethylamino). For the 30 avoidance of doubt substituents may also be on any heteroatom.

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Preferably the ring formed by B₁, B₂, B₃ and B₄ is a pyridinediyl, wherein B₁, or B₃ is a nitrogen atom, pyrimidinediyl, wherein B₁ and B₂ or B₃ and B₄ are nitrogen atoms, pyridazinediyl, wherein B₁, B₃ and B₄ or B₁, B₂ and B₃ are nitrogen atoms. Of these pyridinediyl and pyrimidinediyl are preferred.

5 In one aspect the ring containing B₁, B₂, B₃ and B₄ is unsubstituted. In another aspect the ring containing B₁, B₂, B₃ and B₄ is substituted by one or two substituents selected from hydroxy, carboxy, (1-4C)alkoxycarbonyl or one of the following:

-(CH₂)_n-R, -(CH₂)_n-NRR₁, -CO-R, -CO-NRR₁, -(CH₂)_n-CO-R and -(CH₂)_n-CO-NRR₁:

10

wherein n is 1 or 2;

R and R₁ are independently selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl and (1-4C)alkoxycarbonyl- (1-4C)alkyl or where possible R and R₁ may together form a 5- or 6-membered optionally 15 substituted heterocyclic ring which may include in addition to the nitrogen atom to which R and R₁ are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur.

In a particular aspect the heterocyclic rings formed by R and R₁ are preferably selected from pyrrolidin-1-yl, imidazolin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-morpholino and 4-thiomorpholino. In a particular aspect the heterocyclic ring formed by R and R₁ may be 20 unsubstituted. In an alternative aspect the ring formed by R and R₁ is substituted by 1 or 2 substituents selected from oxo, hydroxy and carboxy.

In a particular aspect, when T₁ is CH or N, X₁ is CO, SO₂, or CH₂ or, when T₁ is CH, X₁ in addition is O or S. Preferably X₁ is CO.

T₁ is CH or N and T₂ is CH or N with the proviso that at least one of T₁ and T₂ is N. 25 For the avoidance of doubt T₁ is directly attached to the groups X₁ and L₁ and T₂ is directly attached to the groups L₁ and X₂.

L₁ is C₁₋₄alkylene for example methylene, ethylene or propylene or is C₁₋₃alkylenecarbonyl for example methylenecarbonyl (-CH₂CO-).

In one aspect R₂ is hydrogen or C₁₋₄alkyl for example methyl or ethyl. In one aspect 30 R₃ is hydrogen or C₁₋₄alkyl for example methyl or ethyl.

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In a preferred aspect R_2 and R_3 are joined to form a C_{1-4} alkylene group, for example a methylene, ethylene or propylene group, or a methylenecarbonyl (- CH_2CO -) group.

In a particular aspect R_2 and R_3 are joined to form, together with T_1 , T_2 and L_1 , a heterocyclic ring wherein at least one of T_1 and T_2 is N. Examples of such heterocyclic rings 5 are piperazine (wherein T_1 and T_2 are both N), piperidine (wherein either T_1 or T_2 is N and the other is CH) and pyrrolidine (wherein either T_1 or T_2 is N and other is CH).

In one aspect the heterocyclic ring formed by T_1 , T_2 , L_1 , R_2 and R_3 is unsubstituted. In another aspect this ring is substituted by one or two substituents selected from hydroxy, 10 oxo, carboxy, ($1-4C$)alkoxycarbonyl or one of the following;

10

-(CH_2)_n-R, -(CH_2)_n-NRR₁, -CO-R, -CO-NRR₁, -(CH_2)_n-CO-R and -(CH_2)_n-CO-NRR₁;

wherein n is 1 or 2;

R and R₁ are independently selected from hydrogen, ($1-4C$)alkyl, ($2-4C$)alkenyl, 15 ($2-4C$)alkynyl, hydroxy($1-4C$)alkyl, carboxy($1-4C$)alkyl and ($1-4C$)alkoxycarbonyl- ($1-4C$)alkyl or where possible R and R₁ may together form a 5- or 6-membered optionally substituted heterocyclic ring which may include in addition to the nitrogen atom to which R and R₁ are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur.

In a particular aspect the heterocyclic rings formed by R and R₁ are preferably 20 selected from pyrrolidin-1-yl, imidazolin-1-yl, piperidin-1-yl, piperazin-1-yl, 4-morpholino and 4-thiomorpholino. In a particular aspect the heterocyclic ring formed by R and R₁ may be unsubstituted. In an alternative aspect the ring formed by R and R₁ is substituted by 1 or 2 substituents selected from oxo, hydroxy, carboxy and ($1-4C$)alkyl, preferably oxo, hydroxy, and carboxy.

25 In a particular aspect X₂ is SO₂, CH₂ or CO. Preferably X₂ is SO₂.

In one aspect Q is unsubstituted. In another aspect Q is substituted by one, two or three substituents selected from halo, trifluoromethyl, trifluoromethoxy, cyano, hydroxy, amino, nitro, trifluoromethanesulphonyl, carboxy, carbamoyl, ($1-4C$)alkyl, ($2-4C$)alkenyl, ($2-4C$)alkynyl, ($1-4C$)alkoxy, ($2-4C$)alkenyloxy, ($2-4C$)alkynyloxy, ($1-4C$)alkylthio, 30 ($1-4C$)alkylsulphanyl, ($1-4C$)alkylsulphonyl, ($1-4C$)alkylamino, di-($1-4C$)alkylamino, ($1-4C$)alkoxycarbonyl, N-($1-4C$)alkylcarbamoyl, N,N-di-($1-4C$)alkylcarbamoyl,

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(2-4C)alkanoyl, (2-4C)alkanoylamino, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, benzyl, benzoyl,

5 heteroaryloxy, heteroarylthio, heteroarylsulphinyl and heteroarylsulphonyl, and wherein said heteroaryl substituent or the heteroaryl group in a heteroaryl-containing substituent comprises a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur, and wherein said phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphinyl, phenylsulphonyl, heteroaryloxy, heteroarylthio, heteroarylsulphinyl,

10 heteroarylsulphonyl, benzyl or benzoyl substituent optionally bears 1, 2 or 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (2-4C)alkanoylamino.

A suitable value for Q when it is naphthyl is, for example, 1-naphthyl or 2-naphthyl;

15 when it is phenyl-(1-4C)alkyl is, for example, benzyl, phenylethyl and 3-phenylpropyl, when it is phenyl-(2-4C)alkenyl is, for example, styryl, cinnamyl or 3-phenylprop-2-enyl; and when it is phenyl-(2-4C)alkynyl is, for example, 2-phenylethynyl, 3-phenylprop-2-ynyl and 3-phenylprop-1-ynyl.

A suitable value for Q when it is a heterocyclic moiety containing up to 4 heteroatoms selected from nitrogen, oxygen and sulphur is, for example, a 5- or 6-membered heterocyclic moiety which is a single ring or is fused to one or two benzo rings such as furyl, benzofuranyl, tetrahydrofuryl, chromanyl, thienyl, benzothienyl, pyridyl, piperidinyl, quinolyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolyl, 1,2,3,4-tetrahydroisoquinolinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pyrrolyl,

20 pyrrolidinyl, indolyl, indolinyl, imidazolyl, benzimidazolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, morpholinyl, 4H-1,4-benzoxazinyl, 4H-1,4-benzothiazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl, thiadiazolyl, tetrazolyl, dibenzofuranyl and dibenzothienyl, which may be attached through any available position including, for an appropriate X₂ group such as, for example,

25 SO₂, C(R⁵)₂ or CO, through any available nitrogen atom. Q may optionally bear up to three substituents including a substituent on any available nitrogen atom.

A suitable value for the heteroaryl substituent on Q or the heteroaryl group in a heteroaryl-containing substituent on Q which comprises a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from oxygen, nitrogen and sulphur is, for example, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, imidazolyl, 5 pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, furazanyl and thiadiazolyl which may be attached through any available position including through any available nitrogen atom.

Suitable values for optional substituents for the ring formed on Q are:

for (1-4C)alkyl: methyl, ethyl and propyl;

10 for (1-4C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for N-(1-4C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

15 for N,N-di-[(1-4C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

for 4-(1-4C)alkylpiperazin-1-ylcarbonyl: 4-methylpiperazin-1-ylcarbonyl and 4-ethylpiperazin-1-ylcarbonyl;

20 for hydroxy-(1-4C)alkyl: hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl;

for (1-4C)alkoxy-(1-4C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

25 for carboxy-(1-4C)alkyl: carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;

for (1-4C)alkoxycarbonyl-(1-4C)alkyl: methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl,

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for carbamoyl-(1-4C)alkyl:
5
for N-(1-4C)alkylcarbamoyl-(1-4C)alkyl:
10
for N,N-di-[(1-4C)alkyl]carbamoyl-
15 (1-4C)alkyl:
20
for pyrrolidin-1-ylcarbonyl-(1-4C)alkyl:
25
for piperidinocarbonyl-(1-4C)alkyl:
30
for morpholinocarbonyl-(1-4C)alkyl:
35
3-methoxycarbonylpropyl and
3-ethoxycarbonylpropyl;
carbamoylmethyl, 1-carbamoylethyl,
2-carbamoylethyl and
3-carbamoylpropyl;
N-methylcarbamoylmethyl,
N-ethylcarbamoylmethyl,
N-propylcarbamoylmethyl,
1-(N-methylcarbamoyl)ethyl,
1-(N-ethylcarbamoyl)ethyl,
2-(N-methylcarbamoyl)ethyl,
2-(N-ethylcarbamoyl)ethyl and
3-(N-methylcarbamoyl)propyl;
N,N-dimethylcarbamoylmethyl,
N-ethyl-N-methylcarbamoylmethyl,
N,N-diethylcarbamoylmethyl,
1-(N,N-dimethylcarbamoyl)ethyl,
1-(N,N-diethylcarbamoyl)ethyl,
2-(N,N-dimethylcarbamoyl)ethyl,
2-(N,N-diethylcarbamoyl)ethyl and
3-(N,N-dimethylcarbamoyl)propyl:
pyrrolidin-1-ylcarbonylmethyl,
1-(pyrrolidin-1-ylcarbonyl)ethyl and
2-(pyrrolidin-1-ylcarbonyl)ethyl;
piperidinocarbonylmethyl,
1-(piperidinocarbonyl)ethyl and
2-(piperidinocarbonyl)ethyl;
morpholinocarbonylmethyl,
1-(morpholinocarbonyl)ethyl and
2-(morpholinocarbonyl)ethyl;

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for piperazin-1-ylcarbonyl-(1-4C)alkyl:

piperazin-1-ylcarbonylmethyl,
1-(piperazin-1-ylcarbonyl)ethyl and
2-(piperazin-1-ylcarbonyl)ethyl;

for 4-(1-4C)alkylpiperazin-1-ylcarbonyl-

5 (1-4C)alkyl:

4-methylpiperazin-1-ylcarbonylmethyl,
4-ethylpiperazin-1-ylcarbonylmethyl,
2-(4-methylpiperazin-1-ylcarbonyl)-
ethyl and 2-(4-ethylpiperazin-1-
ylcarbonyl)ethyl.

10

For suitable value for a (1-4C)alkyl group which may be present on a heterocyclic group in a substituent on L, or the ring formed when R₂ and R₃ are linked is, for example, methyl, ethyl or propyl.

15 Suitable values for substituents (where applicable) which may be present on a heterocyclic or phenyl group within a substituent on Ar, on Q or on a phenyl- or heteroaryl-containing substituent on Q include, for example:-

for halo:

fluoro, chloro, bromo;

20 for (1-4C)alkyl:

methyl, ethyl, propyl, butyl;

for (1-4C)alkoxy:

methoxy, ethoxy;

for (1-4C)alkylamino:

methylamino, ethylamino;

for di-(1-4C)alkylamino:

dimethylamino, diethylamino;

for (2-4C)alkenyl:

vinyl and allyl;

25 for (2-4C)alkynyl:

ethynyl and prop-2-ynyl;

for (2-4C)alkenyloxy:

vinyloxy and allyloxy;

for (2-4C)alkynyoxy:

ethynyoxy and prop-2-ynyoxy;

for 4-(1-4C)alkylpiperazin-1-yl:

4-methylpiperazin-1-yl and

4-ethylpiperazin-1-yl;

30 for (1-4C)alkylthio:

methylthio, ethylthio and propylthio;

for (1-4C)alkylsulphinyl:

methylsulphinyl, ethylsulphinyl and

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for (1-4C)alkylsulphonyl: propylsulphinyl;
methylsulphonyl, ethylsulphonyl and propylsulphonyl;

for (2-4C)alkanoylamino: acetamido, propionamido and butyramido;

5 for (1-4C)alkanesulphonamido: methanesulphonamido and ethanesulphonamido;

for (1-4C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

10 for N-(1-4C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[(1-4C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

15 for 4-(1-4C)alkylpiperazin-1-ylcarbonyl: 4-methylpiperazin-1-ylcarbonyl and 4-ethylpiperazin-1-ylcarbonyl;

for (1-4C)alkanesulphonamidocarbonyl: methanesulphonamidocarbonyl and ethanesulphonamidocarbonyl;

for (2-4C)alkanoyl: acetyl, propionyl and butyryl;

20 for hydroxy-(1-4C)alkyl: hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl;

for (1-4C)alkoxy-(1-4C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

25 for carboxy-(1-4C)alkyl: carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;

for (1-4C)alkoxycarbonyl-(1-4C)alkyl: methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl,

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2-methoxycarbonylethyl,
 2-ethoxycarbonylethyl,
 3-methoxycarbonylpropyl and
 3-ethoxycarbonylpropyl;
 carbamoylmethyl, 1-carbamoylethyl,
 2-carbamoylethyl and 3-carbamoylpropyl;
N-methylcarbamoylmethyl,
N-ethylcarbamoylmethyl,
N-propylcarbamoylmethyl,
 1-(N-methylcarbamoyl)ethyl,
 1-(N-ethylcarbamoyl)ethyl,
 2-(N-methylcarbamoyl)ethyl,
 2-(N-ethylcarbamoyl)ethyl and
 3-(N-methylcarbamoyl)propyl;

10 15 for N,N-di-[(1-4C)alkyl]carbamoyl-(1-4C)alkyl:
N,N-dimethylcarbamoylmethyl,
N-ethyl-N-methylcarbamoylmethyl,
N,N-diethylcarbamoylmethyl,
 1-(N,N-dimethylcarbamoyl)ethyl,
 1-(N,N-diethylcarbamoyl)ethyl,
 2-(N,N-dimethylcarbamoyl)ethyl,
 2-(N,N-diethylcarbamoyl)ethyl and
 3-(N,N-dimethylcarbamoyl)propyl;

20 A preferred class of compounds of the present invention is that wherein:
 25 A is pyridyl, pyrimidinyl or pyridazinyl;
 B is pyridinediyl, pyrimidinediyl or pyridazinediyl;
 X₁ is CO, SO₂ or CH₂, ideally CO;
 T₁ and T₂ are both N;
 L₁ is ethylene or propylene;
 30 R₂ and R₃ are joined to form an ethylene or propylene or methylenecarbonyl group;
 wherein the heterocyclic ring formed by T₁, T₂, L₁, R₂ and R₃ is unsubstituted or is substituted;

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X_2 is SO_2 ;

Q is styryl optionally substituted (preferably 4-substituted), naphthyl optionally substituted (preferably 6-substituted) or is phenyl optionally substituted (preferably 4-substituted) by fluoro, chloro or bromo;

5 and pharmaceutically-acceptable salts thereof.

A particular compound of the invention is:

1-(6-bromonaphth-2-ylsulphonyl)-4-[6-(4-pyridyl)-nicotinoyl]piperazine;

1-(6-bromonaphth-2-ylsulphonyl)-4-[6-(4-pyridyl)-pyridazin-3-ylcarbonyl]piperazine;

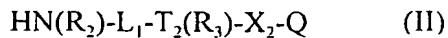
10 1-(6-bromonaphth-2-ylsulphonyl)-4-[5-(4-pyridyl)-2-pyridylcarbonyl]piperazine; or
1-(6-chloronaphth-2-ylsulphonyl)-4-[5-(4-pyridyl)-2-pyridylcarbonyl]piperazine.

Compounds of formula I. or pharmaceutically-acceptable salt thereof. may be prepared by any process known to be applicable to the preparation of related compounds. Such procedures are provided as a further feature of the invention and are illustrated by the 15 following representative processes in which, unless otherwise stated A, B₁, B₂, B₃, B₄, X₁, T₁, T₂, L₁, R₂, R₃, X₂ and Q have any of the meanings defined hereinbefore wherein any functional group, for example amino, alkylamino, carboxy or hydroxy, is optionally protected by a protecting group which may be removed when necessary.

Necessary starting materials may be obtained by standard procedures of organic 20 chemistry.

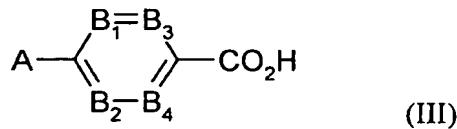
According to another aspect, the present invention provides a process for preparing a compound of formula I or a pharmaceutically acceptable salt thereof, which comprises:

(a) For the production of compounds of the formula (I) wherein T₁ is N and X₁ is CO. 25 the reaction, conveniently in the presence of a suitable base, of an amine of formula (II)



with an acid of the formula (III)

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or a reactive derivative thereof.

A suitable reactive derivative of an acid of formula (III) is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid 5 chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated amide such as 1,1'-carbonyldiimidazole; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole or N-10 hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide.

15 The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic 20 amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a 25 temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or tert-butoxycarbonyl group, an

- 14 -

arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl, or an arylmethyl, for example benzyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be 5 removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for 10 example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). An arylmethyl, such as benzyl may be removed by hydrogenation over a catalyst such as palladium-on-carbon. A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example 15 dimethylaminopropylamine, or with hydrazine.

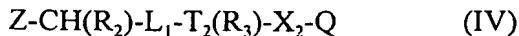
A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl 20 group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying 25 group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

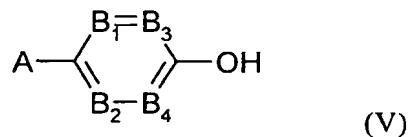
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(b) For the production of those compounds of formula I wherein T₁ is CH and X₁ is O by the reaction, conveniently in the presence of a suitable coupling agent, of a compound of the formula (IV):

5



wherein Z is a displaceable group, with a compound of formula (V):



10

A suitable value for the displaceable group Z is, for example, a halogeno or sulphonyloxy group, for example a fluoro, chloro, bromo, mesyloxy or 4-tolylsulphonyloxy group.

A suitable reagent for the coupling reaction when Z is a halogeno or sulphonyloxy group is, for example, a suitable base, for example, an alkali or alkaline earth metal carbonate, hydroxide or hydride, for example sodium carbonate, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride. The alkylation reaction is preferably performed in a suitable inert solvent or diluent, for example N,N-dimethylformamide.

20 N,N-dimethylacetamide, dimethylsulphoxide, acetone, 1,2-dimethoxyethane or tetrahydrofuran, and at a temperature in the range, for example, -10° to 150°C, conveniently at or near ambient temperature.

An analogous procedure may be employed for the preparation of those compounds of the formula (I) wherein T₁ is CH and X₁ is a group of the formula S.

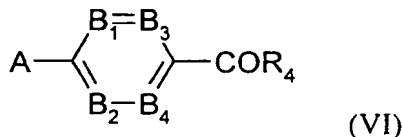
25 A suitable reagent for the coupling reaction of the alcohol of the formula (V) wherein Z is a hydroxy group, where the hydroxy group is converted *in situ* to a displaceable group as defined above, is, for example, the reagent obtained when said alcohol is reacted with a di-(1-4C)alkyl azodicarboxylate in the presence of a triarylphosphine or

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tri-(1-4C)alkylphosphine, for example with diethyl azodicarboxylate in the presence of triphenylphosphine or tributylphosphine. The reaction is preferably performed in a suitable inert solvent or diluent, for example acetone, 1,2-dimethoxyethane or tetrahydrofuran, and at a temperature in the range, for example, 10° to 80°C, conveniently at or near ambient 5 temperature.

(c) For the production of those compounds of formula (I) wherein T₁ is N and X₁ is CH(R₄), the reductive amination of a keto compound of formula (VI):

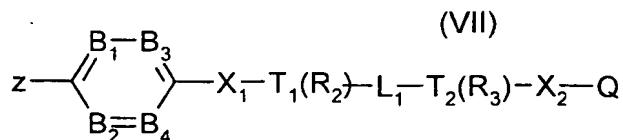
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with an amine of the formula (II) as defined above.

Any reducing agent known in the art for promoting a reductive amination reaction may be employed. A suitable reducing agent is, for example, a hydride reducing agent, for 15 example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents 20 such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride. The reaction is performed at a temperature in the range, for example, 10° to 80°C, conveniently at or near ambient temperature.

25 (d) The reaction of a compound of formula (VII):



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wherein Z is a displaceable group such as halo, with an activated derivative of heterocyclic ring A. Suitable activated derivatives include metalised derivatives, such as with zinc or tin, and borane derivatives. The activated derivative of heterocyclic ring A is reacted with a compound of formula (VII) to effect cross coupling where Z is a halo group, such as iodo. 5 bromo or chloro and triflate. Suitably the reaction is catalysed by use of a transition state metal catalyst, such as palladium, e.g. tetrakis (triphenylphosphine) palladium (0).

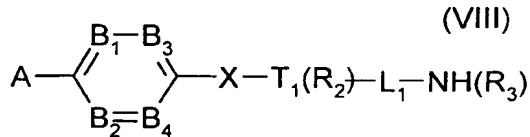
Alternatively it is possible that ring A contains the displaceable group Z and the ring containing B₁ to B₄ is activated, as described above.

Compounds of formula (VII) not suitable for this method are those which contain 10 halo substituents on A, B, or L₁.

(e) By forming A ring on compounds of formula (VII), wherein Z is a functional group capable of cyclisation. Suitable reagents and conditions are described below in the preparation of compounds of formula (X) by cyclisation.

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(f) For the production of compounds wherein T₂ is N, the reaction of a compound of the formula (VIII):



20

with a compound of the formula (IX):

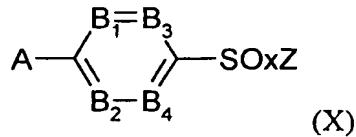


25 wherein Z is a displaceable group for example chloro, under conditions similar to those of process variant (a) above.

(g) For the production of compounds wherein T₁ is N and X₁ is SO or SO₂, the reaction of a compound of the formula (II) as defined above:

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with a compound of the formula (X):



wherein X is one or two and Z is a displaceable group; under appropriate conventional coupling conditions, similar to those of process variant (a) above.

5

(h) For producing compounds of formula I by coupling T₂ to Q and thus preparing the -T₂-X₂-Q moiety, methods analogous to those described in process variants (a), (c) and (f) for preparing the B-X₁-T₁- moiety may be employed.

10 (i) For the production of compounds of the formula (I) wherein X₁ is a group of the formula SO, SO₂, wherein the ring containing B₁ to B₄ bears a 1-oxothiomorpholino or 1,1-dioxothiomorpholino group or a substituent which contains a (1-4C)alkylsulphanyl, (1-4C)alkylsulphonyl, 1-oxothiomorpholino or 1,1-dioxothiomorpholino group, wherein X₂ is a group of the formula SO or SO₂, wherein Q bears a (1-4C)alkylsulphanyl,

15 (1-4C)alkylsulphonyl, phenylsulphanyl, phenylsulphonyl, heteroarylsulphanyl or heteroarylsulphonyl group, the oxidation of the corresponding compound of the formula I wherein X₁, X₂, or both X₁ and X₂ is S.

A suitable oxidising agent is, for example, any agent known in the art for the oxidation of thio to sulphanyl and/or sulphonyl, for example, hydrogen peroxide, a peracid

20 (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxysulphate (such as potassium peroxymonosulphate), chromium trioxide or gaseous oxygen in the presence of platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidising agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a

25 suitable solvent or diluent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature, for example, at or near ambient temperature, that is in the range 15 to 35°C. Suitable reagents and conditions are described in, for example, Page G. O.; Synth. Commun. 23, (1993) 6, 765-769. When a compound carrying a sulphanyl group is required a milder oxidising agent may also be used, for example sodium

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or potassium metaperiodate, conveniently in a polar solvent such as acetic acid or ethanol. It will be appreciated that when a compound of the formula I containing a sulphonyl group is required, it may be obtained by oxidation of the corresponding sulphanyl compound as well as of the corresponding thio compound. Those compounds of formula I which contain 5 oxygen labile groups (such as A ring is pyridyl) are probably not suitable intermediates for this process step, unless oxidation of such groups is desired.

Compounds of formula (II) where T₂ is N may be prepared by the reaction of a compound of the formula (XI)

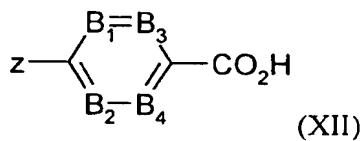
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wherein P is a protecting group, with a compound of formula (IX), as defined above, in an analogous manner as described above in method (e) above, and subsequently removing the 15 protecting group. In addition compounds of formula (II) may be prepared in an analogous manner as described above in methods (g) and (h).

Compounds of formula (IV) may be prepared in an analogous manner as described for the preparation of compounds of formula (II).

Compounds of formula (III) may be prepared by the coupling of a compound of 20 formula (XII), wherein Z is a displaceable group, preferably halo.



with an activated derivative of the heterocyclic ring A via a coupling reaction as described in 25 method (d) above. Ideally the reaction is catalysed, such as with a palladium catalyst. Suitable reagents and conditions are described in a review article Harvey R.G. *Organic Prepearations and Procedures International*, Vol.29,(1997), 139.

Activated derivatives of heterocyclic ring A include metalised derivatives, such as with zinc or tin, borane derivatives and stannyli derivatives. Formation of the activated form

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desired is typically by substitution reactions. The activating group is added to the ring in place of a suitable leaving group or atom, such as halo or triflate. Suitable reagents and conditions are described in Shikara M. et.al.; Chem. Pharm. Bull.; 33(11), 4755-4763 (1985); Sandosham J. et.al.; Heterocycles, Vol.37, No.1, p501, (1994); and Salamoto T. S. et.al.; Tetrahedron; Vol.49, No.43, 9713-9720, (1993).

Alternatively compounds of formula (III) may be prepared by forming A rings on compounds of formula (XII) by cyclisation reaction, wherein Z is a functional group capable of cyclisation. Suitable reagents and conditions are described in Bredereck H. Chem.Ber.; 96, 1505, (1963); Fuchigami, T., Bull. Chem. Soc. Jpn., 49, p3607, (1976); Huffman, K.R.. 10 J. Org. Chem., 28, p1812, (1963); Palusso, G., Gazz. Chim. Ital., 90, p1290, (1960) and Ainsworth C.J., Heterocycl. Chem., 3, p470, (1966). Processes suitable for synthesis of starting materials in such cyclisation reactions are described in Zhang M.Q. et.al; J.Heterocyclic. Chem.; 28, 673, (1991) and Kosugi, M. et al.. Bull. Chem. Soc. Jpn., 60, 767-768 (1987).

15 Compounds of formula (XII) may be prepared via ring formation, such as described in Church R. et.al.; J.Org.Chem., 60, 3750-3758, (1995) and Falck-Penderson M.L. et.al.; Acta Chem. Scand., 47, 63-67, (1993). Compounds formed by such reactions are also suitable starting materials for preparation of activated derivatives of the heterocyclic ring A. as described above.

20 Compounds of formula (V), (VI) and (X) may be prepared in an analagous manner as described for preparing compounds of formula (III). and if required with the use of suitable protecting groups.

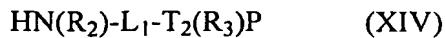
Compounds of formula (VII) wherein T₂ is N may be prepared by the reaction of a compound of the formula (XIII)

25 ZB-X₁-T₁(R₂)-L₁-NH(R₃) (XIII)

with a compound of formula (IX), as defined above, in an analogous manner as described above in method (f).

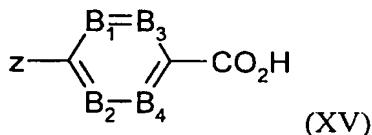
30 Compounds of formula (XIII) wherein T₁ is N and X₁ is CO may be prepared by the reaction of a compound of the formula (XIV)

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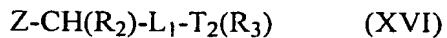
wherein when T_2 is CH then P is H or when T_2 is N then P is a protecting group, with a compound of the formula (XV)

5



in an analogous manner is described in method (a) above and subsequently, where P is a protecting group, effecting removal of the protecting group.

10 Compounds of formula (XIII) wherein T_1 is CH and X_1 is O may be prepared by the reaction of a compound of formula (XVI)



15 wherein Z is a displaceable group with phenol in an analogous method as described in method (b) above

Compounds of formula (X), where x is 1 or 2, may be prepared by oxidation of compound of formula (X), where X_2 is S , in an analogous method as described in method (h) above. Suitable reagents and conditions are described in Newman, M.S., et. al., *Organic*

20 *Synthesis*. Vol. 51, p139. Methods for preparation of the thio analogues of Q are described in Kharasch, N. et. al., *J. Am. Chem. Soc.*, 73, p3240, (1951).

When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with a suitable acid or base using a conventional procedure.

25 When an optically active form of a compound of the formula I is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure, for example by the formation of diastereomeric salts, use of

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chromatographic techniques, conversion using chirally specific enzymatic processes, or by addition of temporary extra chiral group to aid separation.

As stated previously, the compounds of the formula I are inhibitors of the enzyme Factor Xa. The effects of this inhibition may be demonstrated using one or more of the 5 standard procedures set out hereinafter:-

a) Measurement of Factor Xa Inhibition

An in vitro assay system is carried out based on the method of Kettner *et al.*, J. Biol. Chem., 1990, 265, 18289-18297, whereby various concentrations of a test compound are dissolved 10 in a pH7.5 buffer containing 0.5% of a polyethylene glycol (PEG 6000) and incubated at 37°C with human Factor Xa (0.001 Units/ml, 0.3 ml) for 15 minutes. The chromogenic substrate S-2765 (KabiVitrum AB, 20 μ M) is added and the mixture is incubated at 37°C for 20 minutes whilst the absorbance at 405 nm is measured. The maximum reaction velocity (V_{max}) is determined and compared with that of a control sample containing no test 15 compound. Inhibitor potency is expressed as an IC₅₀ value.

b) Measurement of Thrombin Inhibition

The procedure of method a) is repeated except that human thrombin (0.005 Units/ml) and the chromogenic substrate S-2238 (KabiVitrum AB, 7 μ M) are employed.

c) Measurement of Anticoagulant Activity

20 An in vitro assay whereby human, rat or rabbit venous blood is collected and added directly to a sodium citrate solution (3.2 g/100 ml, 9 parts blood to 1 part citrate solution). Blood plasma is prepared by centrifugation (1000 g, 15 minutes) and stored at 2-4°C. Conventional prothrombin time (PT) tests are carried out in the presence of various concentrations of a test compound and the concentration of test compound required to double the clotting time, 25 hereinafter referred to as CT2, is determined. In the PT test, the test compound and blood plasma are incubated at 37°C for 10 minutes. Tissue thromboplastin with calcium (Sigma Limited, Poole, England) is added and fibrin formation and the time required for a clot to form are determined.

d) An ex vivo Assay of Anticoagulant Activity

The test compound is administered intravenously or orally to a group of Alderley Park Wistar rats. At various times thereafter animals are anaesthetised, blood is collected and PT coagulation assays analogous to those described hereinbefore are conducted.

e) An in vivo Measurement of Antithrombotic Activity

5 Thrombus formation is induced using an analogous method to that described by Vogel et al., *Thromb. Research*, 1989, 54, 399-410. A group of Alderley Park Wistar rats is anaesthetised and surgery is performed to expose the vena cava. Collateral veins are ligated and two loose sutures are located, 0.7 cm apart, round the inferior vena cava. Test compound is administered intravenously or orally. At an appropriate time thereafter tissue

10 thromboplastin (30 µl/kg) is administered via the jugular vein and, after 10 seconds, the two sutures are tightened to induce stasis within the ligated portion of vena cava. After 10 minutes the ligated tissue is excised and the thrombus therein is isolated, blotted and weighed.

(f) Rat Disseminated Intravascular Coagulation in vivo activity test

15 Fasted male Alderley Park rats (300-450 g) are pre-dosed by oral gavage (5 mls/kg) with compound or vehicle (5% DMSO/PEG200) at various times before being anaesthetised with Intralval® (120 mg/kg i.p.). The left jugular vein and the right carotid artery are exposed and cannulated. A 1 mL blood sample is taken from the carotid canular into 3.2% trisodium citrate. 0.5 mL of the whole blood is then treated with EDTA and used for platelet count determination whilst the remainder is centrifuged (5 mins, 20000g) and the resultant plasma frozen for subsequent drug level, fibrinogen or thrombin antithrombin (TAT) complex determinations. Recombinant human tissue factor (Dade Innovin Cat.B4212-50), reconstituted to the manufacturers specification, is infused (2 mL/kg/hr) into the venous

20 canular for 60 minutes. Immediately after the infusion is stopped a 2 mL blood sample is taken and platelet count, drug level, plasma fibrinogen concentration and TAT complex are determined as before. Platelet counting is performed using a Coulter T540 blood analyser. Plasma fibrinogen and TAT levels are determining using a clotting assay (Sigma Cat.880-B) and TAT ELISA (Behring) respectively. The plasma concentration of the compound is

25 bioassayed using human Factor Xa and a chromogenic substrate S2765 (Kabi), extrapolated from a standard curve (Fragmin) and expressed in Anti-Factor Xa units. The data is analysed as follows; tissue factor-induced reductions in platelet count are normalised with respect to

pre-dose platelet count and drug activity expressed as a percent inhibition of tissue factor-induced thrombocytopenia when compared to vehicle treated animals. Compounds are active if there is statistically significant ($p < 0.05$) inhibition of TF-induced thrombocytopenia.

5 In general compounds of the formula I possess activity at the following concentrations or doses in at least one of the above tests a) to c):-

test a): IC_{50} (Factor Xa) in the range, for example, 0.001-25 μM ;

test b): IC_{50} (thrombin), for example, greater than 40 μM ;

test c): CT_2 (PT) in the range, for example, 0.1-50 μM .

10 According to a further feature of the invention there is provided a pharmaceutical composition which comprises a heterocyclic derivative of the formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet,
15 capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet
20 or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The amount of active ingredient (that is a heterocyclic derivative of the formula I,
25 or a pharmaceutically-acceptable salt thereof) that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary
30 from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

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According to a further feature of the invention there is provided a heterocyclic derivative of the formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

The invention also includes the use of such an active ingredient in the production of
5 a medicament for use in:-

- (i) producing a Factor Xa inhibitory effect;
- (ii) producing an anticoagulant effect;
- (iii) producing an antithrombotic effect;
- (iv) treating a Factor Xa mediated disease or medical condition;
- 10 (v) treating a thrombosis mediated disease or medical condition;
- (vi) treating coagulation disorders; and/or
- (vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined
hereinbefore or treating a disease or disorder as defined hereinbefore which comprises
15 administering to a warm-blooded animal requiring such treatment an effective amount of an
active ingredient as defined hereinbefore.

The size of the dose for therapeutic or prophylactic purposes of a compound of the
formula I will naturally vary according to the nature and severity of the medical condition,
the age and sex of the animal or patient being treated and the route of administration,
20 according to well known principles of medicine. As mentioned above, compounds of the
formula I are useful in the treatment or prevention of a variety of medical disorders where
anticoagulant therapy is indicated. In using a compound of the formula I for such a purpose,
it will generally be administered so that a daily dose in the range, for example, 0.5 to 500
mg/kg body weight is received, given if required in divided doses. In general lower doses
25 will be administered when a parenteral route is employed, for example a dose for intravenous
administration in the range, for example, 0.5 to 50 mg/kg body weight will generally be
used. For preferred and especially preferred compounds of the invention, in general, lower
doses will be employed, for example a daily dose in the range, for example, 0.5 to 10 mg/kg
body weight.

30 Although the compounds of the formula I are primarily of value as therapeutic or
prophylactic agents for use in warm-blooded animals including man, they are also useful

whenever it is required to produce an anticoagulant effect, for example during the ex-vivo storage of whole blood or in the development of biological tests for compounds having anticoagulant properties.

The compounds of the invention may be administered as a sole therapy or they may 5 be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known 10 anti-hypertensive agent.

The invention will now be illustrated in the following Examples in which, unless otherwise stated:-

- (i) evaporation were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;
- 15 (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;
- (iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were generally performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck,
- 20 Darmstadt, Germany; alternatively high pressure liquid chromatography (HPLC) was performed on a Dynamax C-18 60Å preparative reversed-phase column;
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the end-products of the formula I have satisfactory microanalyses and their 25 structures were confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; unless otherwise stated, CD_3SOCD_3 solutions of the end-products of the formula I were used for the determination of NMR spectral data, chemical shift values were measured on the delta scale; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet;
- 30 (vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, infra-red (IR) or NMR analysis;

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(vii) melting points were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the formula I were generally determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

5 (viii) the following abbreviations have been used:-

DMF N,N-dimethylformamide;
EToAc ethyl acetate;
DMSO dimethylsulphoxide.

10 Example 1

1) 1-(6-bromonaphth-2-ylsulphonyl)-4-[6-(4-pyridyl)-nicotinoyl]piperazine

To a solution of 450mg (1.38mmol) 6-(4-pyridyl)-nicotinic-[4-(1-tert-butyloxycarbonyl)-piperazine]amide in 10ml dry CH_2Cl_2 was added at room temperature 10ml 15 trifluoroacetic acid. The resulting mixture was stirred at room temperature until no further gas evolution was observed. At this point all volatile components were removed under vacuum and the resulting oily gum was dried on the high vacuum pump for 1hour. The intermediate was then re-dissolved in dry dry dichloromethane (15ml). Triethylamine was added until the gas phase above the solution showed an alkaline reaction with wet indicator paper. A further 20 equivalent of triethylamine was added and then 425mg (1.38mmol) of 6-bromonaphth-2-ylsulphonylchloride was added as a solution in dry dichloromethane (2 ml). The resulting homogeneous mixture was stirred at room temperature over night before the reaction was quenched by the addition of 10ml saturated aqueous ammonium chloride. The organic phase was separated and the aqueous phase was extracted three times with dichloromethane (5ml). 25 The combined organic extracts were dried over MgSO_4 , concentrated in vacuo and purified by flash column chromatography on silica (5%MeOH/95% CH_2Cl_2). The purified compound could be re-crystallised from ethyl acetate to yield 440mg of 1-(6-bromonaphth-2-ylsulphonyl)-4-[6-(4-pyridyl)-nicotinoyl]piperazine as a fine pale yellow crystalline solid.
 ^1H NMR (300MHz, CDCl_3) δ = 3.00-3.40 (broad, 4H), δ = 3.48-4.00 (broad, 4H),
30 δ = 7.70-7.78 (m, 2H), δ = 7.80-7.86 (m, 6H), δ = 7.87-7.96 (m, 1H), δ = 8.16-8.17 (m, 1H),
 δ = 8.29-8.32 (m, 1H), δ = 8.62-8.66 (m, 1H), δ = 8.72-8.80 (m, 2H). Solvent peaks Ethyl

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Acetate 1.25 (t), 2.04 (s), 4.12 (q) ~ 6mol%; Dichloromethane 5.3 (s) ~ 3mol%, Water 1.60 (s) unknown amount. MS (ES+) = 537/539 (M+H)⁺, 267, 190, 183, 106, 78. Elemental Analysis: C₂₅H₂₁BrN₄O₃S required C = 55.9, H = 3.9, N = 10.4, Br = 14.9, S = 6.0. found C = 55.3, H = 4.0, N = 10.1, Br = 14.2, S = 5.9, H₂O = 0.1.

5 mp 193.5°C (method DSC)

2) 6-(4-Pyridyl)-nicotinic-[4-(1-tert-butyloxycarbonyl)-piperazine]amide

To a suspension of 834mg (5.67mmol) diethyl-pyridyl-borane in 20ml of degassed, dry tetrahydrofuran was added at room temperature under inert gas atmosphere 637mg (11.3mmol) potassium hydroxide, 1.01g (2.73mmol) Bu₄NI and 1.85g (5.67mmol) 10 6-chloro-nicotinic-[4-(1-tert-butyloxycarbonyl)-piperazine]amide sequentially before 656mg (0.56mmol) of tetrakis (triphenylphosphine) palladium (0) was added. The resulting suspension was heated to 60°C for 2-3 hours. The resulting dark brown suspension was cooled to room temperature before the catalyst was removed by filtration through celite. The 15 filtrate was then diluted with ethyl acetate and washed with 10ml of saturated aqueous sodium chloride solution. The organic phase was separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were treated with charcoal, dried over MgSO₄, concentrated *in vacuo* and purified by flash column chromatography from silica gel (6%MeOH/94%CH₂Cl₂). After purification, 1.68g of the product were obtained as a light 20 brown foam which contained minor impurities and on occasion crystallised very slowly on standing to give a pale brown solid.

¹H NMR (CDCl₃) δ = 1.44 (s, 9H), δ = 3.38-3.82 (broad, 8H), δ = 7.88 (m, 4H), δ = 8.75 (m, 3H). MS (ES+) = 369.4 (M+H)⁺.

25 3) 6-Chloro-nicotinic-[4-(1-tert.-butyloxycarbonyl)-piperazine]amide

To a suspension of 18.7g (118mmol) of 6-chloro nicotinic acid and 22.1g (118mmol) and (1-tert-butyloxycarbonyl)-piperazine in 500ml of dry dichloromethane was added 25g (130mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 36ml (236mmol) dry triethylamine at room temperature. The resulting pale brown solution was

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stirred at room temperature for 16 hours before being quenched by the addition of 50ml saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated *in vacuo* and purified by flash 5 column chromatography from silica gel to yield 30.5g of colourless crystals of the desired 6-chloro-nicotinic-[4-(1-tert-butyloxycarbonyl)-piperazine]amide and some 3.5g of product which was contaminated by unreacted 6-chloro-nicotinicacid.

1H NMR ($CDCl_3$) δ = 1.44 (s, 9H), δ = 2.37-2.56 (broad s, 7H)
 δ = 2.56-2.81 (broad s, 1H), δ = 2.40 (m, 1H), δ = 2.70 (m, 1H), δ = 8.45 (m, 1H). MS (ES+) = 10 651.4 ($2M^+$), 326.4 and 328.4 ($M+H$)⁺.

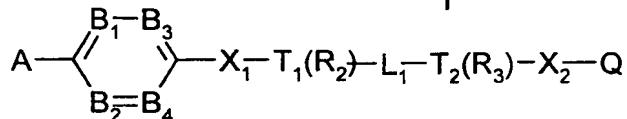
4) Diethyl-pyridyl borane

This reagent was obtained via a modified procedure described in *Chem. Pharm. Bull.* (1985), 33 (11), p.4755

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CLAIMS

1. A compound of the formula I



5

wherein:

A is an optionally substituted 5- or 6-membered monocyclic aromatic ring containing 1, 2 or 3 ring heteroatoms selected from oxygen, nitrogen and sulphur atoms;

B₁, B₂, B₃ and B₄ are independently CH or a nitrogen atom, wherein the ring formed from B₁,

10 B₂, B₃ and B₄ may optionally be substituted; with the proviso that at least one of B₁, B₂, B₃ and B₄ is nitrogen;

T₁ is CH or N;

T₂ is CH or N;

with the proviso that at least one of T₁ and T₂ is N;

15 X₁ is SO, SO₂, C(R₄)₂ or CO when T₁ is CH or N; or in addition X₁ is O or S when T₁ is CH; and wherein each R₄ is independently hydrogen or (1-4C)alkyl;

L₁ is (1-4C)alkylene or (1-3C)alkylenecarbonyl;

R₂ is hydrogen or (1-4C)alkyl;

R₃ is hydrogen or (1-4C)alkyl;

20 or R₂ and R₃ are joined to form a C₁₋₄alkylene or -CH₂CO- group; wherein the ring formed by T₁, R₂, R₃, T₂ and L₁ is optionally substituted;

X₂ is S(O)_y wherein y is one or two, C(R⁵)₂ or CO; and each R⁵ is hydrogen or C₁₋₄alkyl;

Q is phenyl, naphthyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl or a

25 heterocyclic moiety containing up to 4 ring heteroatoms selected from nitrogen, oxygen and sulphur and Q is optionally substituted;

and pharmaceutically acceptable salts thereof.

2. A compound of formula I as claimed in claim 1 wherein Q is either unsubstituted or

30 substituted by one, two or three substituents selected from halo, trifluoromethyl,

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trifluoromethoxy, cyano, hydroxy, amino, nitro, trifluoromethanesulphonyl, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (2-4C)alkenyloxy, (2-4C)alkynyloxy, (1-4C)alkylthio, (1-4C)alkylsulphanyl, (1-4C)alkylsulphonyl, (1-4C)alkylamino, di-(1-4C)alkylamino, 5 (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl, (2-4C)alkanoyl, (2-4C)alkanoylamino, hydroxy-(1-4C)alkyl, (1-4C)alkoxy-(1-4C)alkyl, carboxy-(1-4C)alkyl, (1-4C)alkoxycarbonyl-(1-4C)alkyl, carbamoyl-(1-4C)alkyl, N-(1-4C)alkylcarbamoyl-(1-4C)alkyl, N,N-di-(1-4C)alkylcarbamoyl-(1-4C)alkyl, phenyl, heteroaryl, phenoxy, phenylthio, 10 phenylsulphanyl, phenylsulphonyl, benzyl, benzoyl, heteroaryloxy, heteroarylthio, heteroarylsulphanyl and heteroarylsulphonyl, and wherein said heteroaryl substituent or the heteroaryl group in a heteroaryl-containing substituent comprises a 5- or 6-membered monocyclic heteroaryl ring containing up to 3 heteroatoms selected from nitrogen, oxygen and sulphur, and wherein said phenyl, heteroaryl, phenoxy, phenylthio, phenylsulphanyl, 15 phenylsulphonyl, heteroaryloxy, heteroarylthio, heteroarylsulphanyl, heteroarylsulphonyl, benzyl or benzoyl substituent optionally bears 1, 2 or 3 substituents selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, nitro, carboxy, carbamoyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di-(1-4C)alkylamino, (1-4C)alkoxycarbonyl, N-(1-4C)alkylcarbamoyl, N,N-di-(1-4C)alkylcarbamoyl and (2-4C)alkanoylamino.

20

3. A compound of formula I as claimed in either claim 1 or 2 wherein any ring formed by T_1 , R_2 , R_3 , T_2 is either unsubstituted or substituted by one or two substituents selected from hydroxy, oxo, carboxy, (1-4C)alkoxycarbonyl or one of the following;

25 $-(CH_2)_n-R$, $-(CH_2)_n-NRR_1$, $-CO-R$, $-CO-NRR_1$, $-(CH_2)_n-CO-R$ and $-(CH_2)_n-CO-NRR_1$;

wherein n is 1 or 2;

R and R_1 are independently selected from hydrogen, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, hydroxy(1-4C)alkyl, carboxy(1-4C)alkyl and

30 (1-4C)alkoxycarbonyl(1-4C)alkyl or where possible R and R_1 may together form a

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5- or 6-membered optionally substituted heterocyclic ring which may include in addition to the nitrogen atom to which R and R₁ are attached 1 or 2 additional heteroatoms selected from nitrogen, oxygen and sulphur.

5 4. A compound of formula I as claimed in any of the preceding claims wherein X₁ is CO.

5. A compound of formula I as claimed in any of the preceding claims wherein X₂ is SO₂.

10

6. A compound of formula I as claimed in any of the preceding claims for use in medical therapy.

7. Use of a compound of formula I, as defined in any one of the claims 1 to 5, in the 15 production of a medicament for treating a Factor Xa mediated disease or medical condition.

8. A pharmaceutical composition comprising a compound of formula I, as defined in any one of claims 1 to 5.

20 9. A method of treating a Factor Xa mediated disease or medical condition which comprises administering to a warm-blooded animal requiring such treatment an effective amount of a compound of formula I, as claimed in any one of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

Interr. Application No
PCT/GB 98/02210

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/82 A61K31/455

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 10022 A (ZENECA LTD ;FAULL ALAN WELLINGTON (GB); MAYO COLETTE MARIE (GB); P) 4 April 1996 see page 111; table IV ---	1-9
Y	KUNITADA S ET AL: "FACTOR XA INHIBITORS" CURRENT PHARMACEUTICAL DESIGN, vol. 2, no. 5, October 1996, pages 531-542, XP002057653 see page 539 ---	1-9
P, Y	WO 98 21188 A (TURNER PAUL ;PRESTON JOHN (GB); STOCKER ANDREW (GB); ZENECA LTD (G) 22 May 1998 see page 19-23; claim 1 ---	1-9 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

*** Special categories of cited documents :**

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/GB 98/02210

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 97 28129 A (ZENECA LTD ;SMITHERS MICHAEL JAMES (GB); PRESTON JOHN (GB); STOCKE) 7 August 1997 see page 31-34; claim 1 -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02210

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9610022	A 04-04-1996	AT 168685	T	15-08-1998
		AU 696491	B	10-09-1998
		AU 3530795	A	19-04-1996
		BR 9509045	A	30-09-1997
		CA 2197471	A	04-04-1996
		CZ 9700893	A	16-07-1997
		DE 69503647	D	27-08-1998
		EP 0783500	A	16-07-1997
		ES 2119472	T	01-10-1998
		HU 77769	A	28-08-1998
		JP 10506122	T	16-06-1998
		NO 971415	A	22-05-1997
		PL 319430	A	04-08-1997
		SK 38597	A	10-09-1997
		ZA 9508085	A	24-04-1996
WO 9821188	A 22-05-1998	AU 4874897	A	03-06-1998
WO 9728129	A 07-08-1997	AU 1608597	A	22-08-1997